Claim 1 has also been amended to reflect the fact that Applicants' dispersions must satisfy either an *in vitro* test (in MFD) or an *in vivo* test, which tests reflect an improvement in concentration relative to a control. The amendment is supported at page 5, line 18 to page 6, line 12 (relevant to subsection (a)) and at page 6 lines 16-26 (relevant to subsection (b)). Because these tests have been incorporated into claim 1, claims 5 and 6 have been canceled.

The requirement for a dose to aqueous solubility ratio greater than 100 has been removed from independent claims 1 and 15. The dose to aqueous solubility requirement is now reflected in new dependent claim 53, which is supported by (and represents the re-instatement of) dependent claims 2 and 18 as originally filed, which Applicants had previously canceled.

The requirement in claims 1 and 15 that the dispersion be homogeneous has been removed as redundant of the requirement that the drug be molecularly dispersed and amorphous in the dispersion.

The requirement that the dispersion comprise spray dried particles that are solidified in less than 5 seconds and that have a residual solvent content less than 10 wt% has also been removed from the independent claims. It is noted that dependent claims 49 and 50 reflect preferred embodiments for solidification and residual solvent content.

Claims 39, 41-45, and 47 have been canceled to reduce the issues for consideration. The requirement in each of claims 43, 45, and 47 that the drug be crystalline is now reflected in new claim 54 which depends from claims 1 and 15.

New claims 55 and 56 further limit the drug:polymer ratios of the claimed spray dried solid dispersion.

Claim dependencies have been amended as appropriate so that the remaining claims do not reflect a dependence on any claim that was canceled.

Claims 1, 4, 15, 17, 22-23, 26, 28-38, 49-51 and 53-56 are currently in the application.

The rejections and Applicants' traversal

The claims continue to be rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (English Translation of Yakuzaigaku 53(4): 221-228, 1993). The Examiner described the difference between Applicants' invention and Yamaguchi as follows:

> The difference between Yamaguchi and the instant claims is that Yamaguchi is silent on the amount of residual solvent present after the spray drying process. However, it is the Examiner's position that since the prior art does not explicitly disclose that there is zero residual solvent present or greater than 10 wt% residual solvent present after spray drying, it is reasonable to expect that some amount of solvent is left after spray drying and the person of ordinary skill in the art would have the technical know how to determine residual solvent left after spray drying.

Office Action at page 4, lines 1-6 of first full paragraph. The Examiner additionally appeared to contend that Yamaguchi discloses HPMCAS (AQOAT®) dispersions within the scope of Applicants' claims:

> Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQOAT dispersion. Specifically, paragraph 2, page 2 of translation states "MAT(100 g) and 50 g, 20 g, 10 g or 5 g of CMEC were dissolved in 300 ml, of a 1:1 solvent mixture of methylene chloride and ethanol, then spray-dried (SD-1; Tokyo Rikakikai) at an inlet temperature of 120 °C to form a powder. **Preparation was similarly carried out using AQOAT®** or EC as the carrier." Thus drug: polymer ratios of from 2:1, 5:1, 10:1 and 20:1 are disclosed.

Office Action, text bridging pages 3 and 4, emphasis in the Office Action itself.

Although Applicants have removed the element of residual solvent from the claims, it is respectfully submitted that Yamaguchi does not anticipate. The claims are novel over and above the element of residual solvent. The following reasoning applies.

Applicants contend that Yamaguchi discloses a single composition of AQOAT and MAT, at a drug:polymer ratio of 10:1, i.e., a drug loading of 91%. That single composition is outside the drug:polymer range of between 1:0.4 (71% drug loading) and 1:20 (5% drug loading) required by Applicants' claims. Applicants distinguish over Yamaguchi because Yamaguchi does not disclose a spray dried composition of drug and polymer within the drug:polymer range of between 1:0.4 and 1:20. Applicants' comments further in support of their position follow.

According to its title, Yamaguchi seeks to improve the pharmaceutical properties of 4''-O-(4-Methoxyphenyl) acetyltylosin by preparing solid dispersions with carboxymethyl ethyl cellulose (CMEC). Thus Yamaguchi primarily relates to the use of CMEC, which is apparent and further supported from reading the document as a whole.

Hence, in the abstract it is stated:

> *The effect of solid dispersion with* ***carboxymethylethylcellulose (CMEC)*** *on the dissolution and absorption of 4''-O-(4-Methoxy-phenyl)acetyltylosin (MAT) has been investigated. Amorphous state of* ***MAT*** *was obtained by spray-drying of dichloromethane-ethanol (1:1) solution of MAT and either CMEC or hydroxypropylmethylcellulose acetate succinate (AQOAT®). Enhanced solubility of MAT and improved stability of MAT amorphous state were observed in* ***MAT-CMEC solid dispersion systems****. In vivo absorption studies were carried out in dogs by measuring the plasma levels of MAT following the oral administration of MAT solid dispersion with* ***CMEC*** *(mixing ratio 10:1) and MAT crystal powder. Using the solid dispersion formulation, effective increases of up to more than 2.5-fold in both AUC and C_{max} were achieved. The increased bioavailability of MAT resulted in the modification of the dissolution characteristics of MAT by preparing* ***the solid dispersion with CMEC****." (emphasis added)*

From these statements, the skilled person would draw the conclusion that hydroxy-propylmethylcellulose acetate succinate (or "AQOAT®") is used only for comparative purposes.

That conclusion is supported by the following passages in Yamaguchi:

The paragraph bridging pages 2 and 3 very briefly describes the preparation of solid dispersions:

> "*The solid dispersion was prepared by a spray drying process. MAT (100 g) and 50 g, 20 g, 10 g or 5 g of CMEC were dissolved in 300 mL of a 1:1 solvent mixture of methylene chloride and ethanol, then spray-dried (SD-1; Tokyo Rikakikai) at an inlet temperature of 120°C to form a powder. Preparation was similarly carried out using AQOAT® or EC as the carrier.*"

While Yamaguchi explicitly mentions MAT/CMEC ratios of 2, 5, 10 and 20, it does not unequivocally disclose solid dispersions comprising AQOAT® and MAT in the same ratios. The exact wording used by Yamaguchi is "preparation was similarly carried out using AQOAT® or EC as the carrier".

Hence, the skilled person would look for further guidance as to exactly which AQOAT®- or EC-containing compositions have been prepared. In doing so, he would come across the "Results and Discussion" section dealing, according to its title, with "solubility of MAT-polymer solid dispersion[s]". It is stated there (at the bottom of page 4) that "dispersion systems (solid dispersion) in which the amorphous MAT was mixed with

the enteric polymers CMEC and AQOAT® were prepared, and the solubilities of these systems were compared with that of amorphous MAT by itself".

Then, at page 5, lines 4 to 10 of Yamaguchi, it is stated:

> "Solid dispersions having MAT/CMEC mixing ratios ranging from 10:5 to 10:20 were prepared, and these dispersions were subjected to powder x-ray diffraction analysis. In each case, a broad halo pattern was obtained, demonstrating that the MAT was in an amorphous state without regard to the mixing ratio of CMEC. Fig. 2 shows the results of solubility tests at pH 4.0 for solid dispersions containing MAT and CMEC or AQOAT® in a ratio of 10:1. The dissolution patterns for amorphous MAT containing no polymer and for a solid dispersion with the water-insoluble polymer EC are also shown as controls."

For the Examiner's convenience, Fig. 2 is reproduced below, noting that the particular polymer used for each dissolution pattern has been added on the right for convenience:

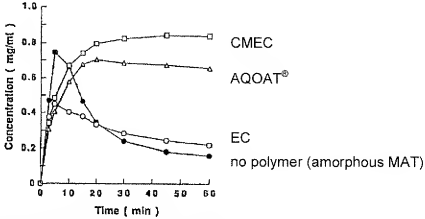

Fig. 2. Dissolution Patterns of MAT from Various Solid Dispersion Systems in Acidic Solution (pH 4.0) at 37.0°C (mixing ratio of MAT and polymer : 10/1)
□ : CMEC, △ : AQOAT®, ○ : EC, ● : amorphous MAT without polymer.

It is apparent from Figure 2 that CMEC modifies the dissolution characteristics of MAT better than AQOAT® (or EC). This is also explicitly stated at the bottom of page 5 of Yamaguchi:

> "The MAT-EC solid dispersion exhibits the same drug dissolution pattern as amorphous MAT by itself. The extremely short duration of the supersaturated state suggests that intermolecular

> interactions between MAT and EC are weak. On the other hand, a decline in concentration like that which occurs for amorphous MAT alone or together with EC was not observed in solid dispersions with the enteric polymers CMEC and AQOAT®; rather, a supersaturated state was maintained for a long period of time. The drug concentration from 30 minutes to 60 minutes after the start of the dissolution test remained essentially constant at **820 µg/mL in the case of CMEC** and at **770 µg/mL in the case of AQOAT®**." (emphasis added)

As the drug concentration is highest with the use of CMEC, this polymer is chosen in the further experiments described in Section 3 of Yamaguchi titled "Change in MAT Solubility with CMEC Content" of the Results and Discussion section. Its introductory portion reads as follows:

> "To study the correlation between the amount of carrier and the solubility **when CMEC is used as the solid dispersion carrier**, solid dispersions composed of MAT and **CMEC** in differing proportions were prepared and the MAT solubility at pH 4.0 for each of the samples was tested. Fig. 4 shows the solubility test results at pH 4.0 for **four different solid dispersion samples**, amorphous MAT containing no CMEC, and MAT crystalline bulk powder." (emphasis added)

The mixing ratios of MAT and CMEC are indicated in Figure 4, which is again, for the Examiner's convenience, reproduced below (the mixing ratios have been added at the right-hand side):

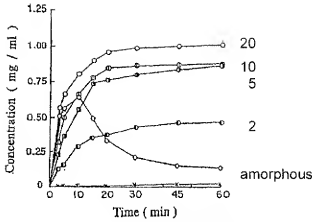

Fig. 4. Dissolution Patterns of MAT from MAT-CMEC Solid Dispersion in Acidic Solution (pH 4.0) at 37.0℃
Mixing ratio of MAT and CMEC : ◐, 10/5; ◑, 10/2; ◔, 10/1 ; ○, 10/0.5; ◇, amorphous MAT without CMEC; ×, crystalline MAT.

The compositions, the dissolution patterns of which are shown in Figure 4 above, are exactly the ones described in Yamaguchi at the bottom of page 2, i.e., solid dispersions comprising 100 g MAT and 50 g, 20 g, 10 g and 5 g of CMEC, respectively.

Thus, in the light of the examples described in Yamaguchi, the passage "preparation was similarly carried out using AQOAT® or EC as the carrier" would be construed by the skilled person to mean that the dispersions shown in Figure 2 were prepared in a way similar to the preparation of the CMEC solid dispersions. The AQOAT® dispersion of Figure 2 contains MAT and AQOAT® in a ratio of 10:1 (see page 5, line 8), which ratio is far above the range specified in claim 1 as amended.

For the Examiner's convenience, the drug-to-polymer ratios for the polymers disclosed in Yamaguchi and for the present invention are summarized below:

Drug	Drug-to-Polymer Ratio	
	Yamaguchi	Invention
CMEC	2, 5, 10, 20	–
EC	10	
AQOAT®	10	0.05-2.5

In summary, and as demonstrated above, the claimed composition cannot be anticipated by Yamaguchi who discloses only a single (10/1) AQOAT/MAT composition, which is well outside the compositional range required by Applicants.

The Examiner has continued to reject the claims for obviousness over Yamaguchi. The rejection is traversed on the basis that Yamaguchi teaches away from Applicants' invention, and also fails to teach a dispersion that is molecularly dispersed and in which the drug is amorphous.

As can be seen from the table above, the claimed composition differs from the lone Yamaguchi (10/1 MAT:AQOAT) composition in that it has a lower drug-to-polymer ratio or, in other words, a lower drug load. Thus, the claimed drug-to-polymer ratio of 0.05 to 2.5 (1:20 to 1:0.4) corresponds to a drug load of 4.8 to 71.4%. On the other hand, the drug load of the AQOAT®-containing composition disclosed in Yamaguchi is 91%.

The surprising technical effect achieved by the lower drug load according to the present invention is described in the experiments detailed in the Declaration of Dwayne T. Friesen filed with Applicants' previous response (i.e., to the Office Action of August 30, 2005). The experiments in that declaration clearly demonstrate that the dissolution performance of Applicants' dispersions improves as the drug load decreases.

Yamaguchi, to the contrary, does not present one of ordinary skill seeking to achieve an improved dissolution performance with any incentive to use drug loads or drug-to-polymer ratios within Applicants' claimed range.

This is borne out by the following statements on pages 7 to 9 of Yamaguchi:

According to the paragraph below Figure 3 on page 7 (see lines 8/9) "the amount of dissolved drug showed CMEC content dependence, with a higher solubility being exhibited at progressively lower ratios of CMEC addition". In other words, Yamaguchi teaches that a higher solubility can be achieved at lower ratios of CMEC addition or at a higher drug load. This is consistent with the dissolution patterns shown in Figures 4 and 5 on pages 8 and 9 of Yamaguchi having a drug loading of 67%, 83%, 91% and 95%. The highest concentration of the drug (MAT) in solution is achieved by the composition having the highest drug loading of 95%.

Hence, one of ordinary skill seeking to provide compositions having an improved dissolution performance would not seriously contemplate using compositions having a lower drug loading within Applicants' claimed range based on the teachings of Yamaguchi.

Again, this is further borne out by Yamaguchi and, in particular, by the discussion of the dissolution performance of the MAT/CMEC compositions tested in the passage bridging pages 8 and 9:

> "...at pH 4.0, the solid dispersion having **the lowest CMEC content** (MAT and CMEC mixing ratio, 10:0.5) had **the highest drug concentration**, whereas at pH 6.8, this same dispersion had the lowest drug concentration of the four solid dispersions. The solid dispersion having the highest drug concentration at pH 6.8 was that having a mixing ratio of 10:1. Accordingly, to enhance absorption within the gastrointestinal tract, a solid dispersion having a MAT/CMEC mixing ratio of 10:1 was presumably more advantageous at pH 6.8 than a solid dispersion having a ratio of 10:0.5. We are currently looking at why, in solubility tests using JP Solution 2, **solid dispersions having mixing ratios of 10:2.5 and 10:5 had lower drug concentrations than did the 10:1 solid dispersion**;" (emphasis added)

Thus, Yamaguchi clearly teaches away from using low drug-to-polymer ratios such as the above mentioned two ratios of 10:2.5 and 10:5 corresponding to drug loads of 80% and 67%, respectively. According to Yamaguchi, the highest drug concentration is achieved at a mixing ratio of 10:1 (at pH 6.8) and 10:0.5 (at pH 4.0) corresponding to a drug load of 91% and 95%, respectively.

To disregard the clear teaching in Yamaguchi to use high drug-to-polymer ratios and to select lower drug loads to improve the dissolution performance while Yamaguchi teaches the opposite, is clearly unobvious. Accordingly, Applicants respectfully submit that their claimed compositions are unobvious, hence patentable, vis-à-vis Yamaguchi.

The claims continue to be rejected under 35 USC 103(a) as unpatentable over Miyajima et al. (US 4,983,593).

Applicants' respectfully request the Examiner to reconsider in light of the reasoning presented below coupled with the Declaration of Scott B. McCray.

As already mentioned above, the instant claims require that the drug is molecularly dispersed and amorphous in the dispersion. Miyajima mentions the phrase "spray drying" once in the entire specification and never mentions anything about spray drying again. Miyajima does not disclose an actual spray dried dispersion, let alone a solid **amorphous** spray dried dispersion, **or how to achieve one**. In different words, Miyajima simply alludes to "spray drying" without ever teaching how to make a solid **amorphous** dispersion in which the drug is molecularly dispersed.

In this connection, it is important to note that material made by spray drying can contain particles consisting of crystals and/or amorphous solids, depending on the **rate**

and **conditions** of solvent removal. Thus, spray drying does not necessarily produce amorphous drug.

This is borne out by the Remington article (previously submitted) that demonstrates that material made by spray drying can contain particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. The importance of Remington is that it shows that spray drying can produce a crystalline product, rather than that it can produce an amorphous product, coupled with the fact that Miyajima discloses nothing about the importance of "amorphous" or of how to achieve an amorphous dispersion.

Hence, the mere mention of the phrase "spray drying" once in Miyajima does not teach (or make obvious) a solid amorphous dispersion as required by the instant claims. The Remington article clearly shows that spray drying does not necessarily produce amorphous drug. Miyajima does not contain any teaching at all as to how the skilled person would make a polymer/drug dispersion in which the drug is amorphous and as to what factors might be important if one wanted to do so. Given the utter lack of guidance in Miyajima, one of ordinary skill could just as easily make a spray dried material containing crystals, as confirmed in Remington, as make an amorphous dispersion, as required by Applicants' claims. Only the present application has provided such disclosure that details the requirements (see page 15, line 31 to page 16, line 26) and that enables making an amorphous dispersion, and those requirements are reflected in applicant's claims. Miyajima, by contrast, provides no guidance that would lead one to make an amorphous dispersion, as opposed to a spray dried material, that contains crystalline drug per Remington.

Further in support of their position, Applicants herewith submit the Declaration of Scott B. McCray which demonstrates, *inter alia*, that a granulation according to Miyajima example 6 does not form a homogeneous solid amorphous dispersion, as confirmed by differential scanning calorimetry (DSC) and x-ray diffraction (PXRD). In fact, about two-thirds of the drug, nicardipine hydrochloride, was crystalline. See the Declaration at paragraphs 6 and 8. Dissolution tests confirmed that the Miyajima granulation was about two-thirds crystalline and one third amorphous. See the Declaration at paragraph 13. The declaration thus confirms that Miyajima prepared material containing substantial amounts of crystals. Miyajima never describes or provides even the remotest guidance as to how one of ordinary skill would go about producing a dispersion in which the drug is molecularly dispersed and amorphous, as required by Applicants.

Further, Miyajima makes no distinction between dispersions produced, for example, by vacuum evaporation and dispersions as claimed by applicant. Miyajima exemplifies dispersions made using drying in vacuo, but discloses nothing about performance relative to dispersions produced by spray drying according to the present application. Due, inter alia, to the fast solidification time and low residual solvent level used according to the present invention (see page 16, lines 6 to 8 and 13 to 26 of the description), dispersions are made by spray drying such that the drug is molecularly dispersed, which dispersions effect better concentration enhancement than the relatively non-homogeneous dispersions made by a vacuum evaporation method. Applicant has conclusively demonstrated this point in the examples of the description (see applicant's Example 24 and Comparative Example C9; Example 29 and C13 in the instant application). One of ordinary skill would thus not find applicant's solid amorphous dispersions obvious from Miyajima that says nothing about them.

As mentioned above, Miyajima makes no distinction between dispersions produced, for example, by vacuum evaporation and dispersions as claimed by applicant. Thus, Miyajima does not suggest the desirability or incentive to make the modification needed to arrive at the claimed invention.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited. The Commissioner is hereby authorized to charge any additional fees which may be required, or to credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Respectfully submitted,

Date: October 17, 2006

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